# Synthesis, Structure, and Characterization of Polymeric Stationary Phase Derived from (*R,R*)-Tartramide and Bisphenol-S

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**ABSTRACT:**   The preparation of a new chiral polymeric stationary phase for chromatography is presented. A porous copolymer of mono- and dimethacrylate derivatives of bisphenol-S and divinylbenzene containing hydroxyl functional groups was used as a matrix. (3-Aminopropyl)triethoxysilane was used as a coupling agent and was bonded to these groups. The obtained compound was transferred into a final product during a three-step synthesis. The properties of the obtained polymeric phase with the chiral moiety were studied. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 82: 3409–3417, 2001

**Key words:**   chiral porous copolymers; derivative of (*R,R*)-tartramide and bisphenol-S; chromatographic stationary phase

## INTRODUCTION

The development of such sciences as biochemistry and pharmacy disclosed the fact that enantiomers of biologically active compounds show great differences in their biological and metabolic activities toward racemates. Separation of racemates by means of classical methods is time consuming and expensive. Therefore, the development of chromatographic methods, particularly high performance liquid chromatography (HPLC), allowed attempts to be made to separate and purify optical isomers using these methods.

Most chiral phases described in the literature are silica gels modified with chiral fragments.[1] The phases of this type were introduced by Dobashi and Hara,[2] Pirkle and Pochapsky,[1] and

Gasparrini et al.[3] These chiral phases were characterized by good chromatographic effectiveness and applicability on a laboratory scale. Dobashi and Hara[4] reported that (*R,R*)-*N,N′*-diisopropyltartramide functions as a widely applicable chiral mobile-phase additive (CMPA) in silica gel chromatography. This CMPA recognizes the molecular chirality of enantiomers through its dual hydrogen-bond association and is capable of resolving enantiomers containing $\alpha$- or $\beta$-hydroxycarboxylic acid, $\beta$-hydroxyketone, $\beta$-amino alcohol, $\alpha$-amino acid, $\alpha$-hydroxyketoxime, 1,2-diol derivatives, and bi-$\beta$-naphthol.

Studies on the synthesis of chromatographic chiral polymeric packings of high thermal stability and good physicochemical resistance were carried out in our laboratory. An achiral polymer matrix with a homogeneous globule shape with a reactive hydroxyl group was obtained in copolymerization of the mixture of mono- and dimethacrylic esters of bisphenol-S with divinylbenzene.[5] The chromatographic properties of the achiral porous copolymer were studied.[6] An effect
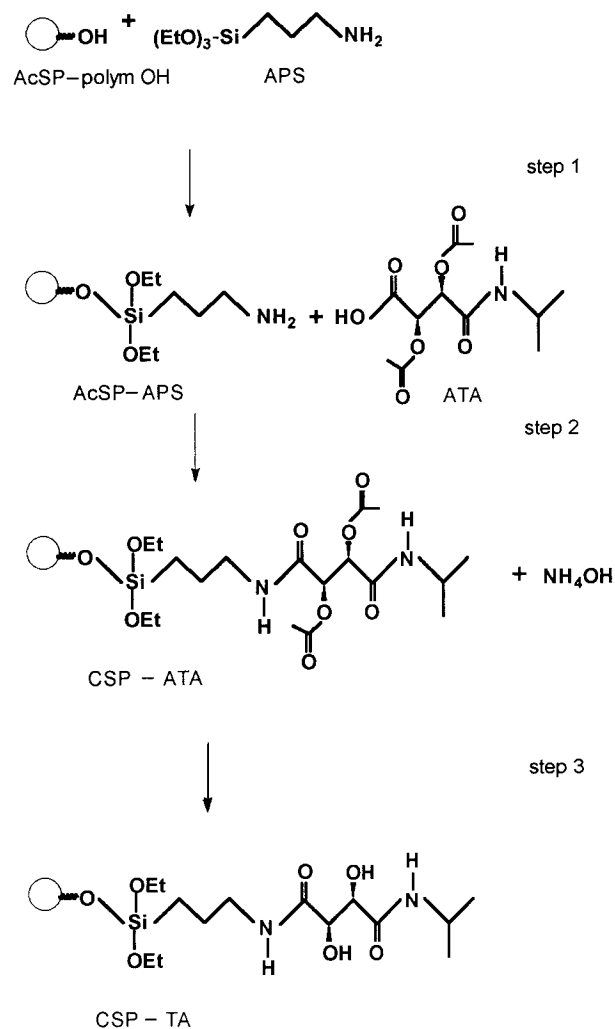
**Scheme 1**

of the functional groups on the packing selectivity was determined using the complete selectivity and selectivity triangle methods. This achiral porous copolymer is presently used for the preparation of chiral packing of the "brush" type.

## EXPERIMENTAL

### Materials

Di-*N*-succinimidyl oxalate (mp 246°C) was obtained by the reaction of *N*-hydroxysuccinimide (Merck) with oxalylchloride (Merck) in toluene.[7] Acetonitrile (Fluka) was distilled from calcium hydride, and toluene (POCh, Gliwice, Poland) was distilled from sodium metal. (*R*,*R*)-Tartaric acid (Merck), isopropylamine (Fluka), and (3-amin-

opropyl)triethoxysilane (APS, Fluka) were reagent grade purity. Reagent grade dichloromethane, acetone, hexane, methanol, acetic anhydride, pyridine, and triethylamine were from POCh.

## Synthesis of Polymeric Chiral Stationary Phase

### *4,4′-Diphenyl Sulfone Dimethacrylate/4-Hydroxydiphenyl Sulfone 4′-Methacrylate-Divinylbenzene (AcSP-polym-OH)*

The synthesis of the polymeric matrix (AcSP-polym-OH) with predating —OH groups was previously described.[5]

### *APS of AcSP-polym-OH (AcSP-APS)*

Three grams of APS were stirred into a suspension containing 5 g of copolymer beads (AcSP-polym-OH) in 10 mL of toluene. The mixture was heated at 110°C for 3 h and then cooled to room temperature. The polymer beads were collected by filtration; washed with acetone (200 mL), water (200 mL), and methanol (200 mL); and dried. There were 5.3 g of modified polymeric beads obtained that contained 1.8% N.

### *(R,R)-N-Isopropyldiacetyltartaric Acid Monoamide (ATA)*

Finely powered (*R*,*R*)-tartaric acid (10.96 g, 77.2 mmol) was converted into (*R*,*R*)-diacetyltartaric acid anhydride using acetic anhydride and then converted into monoamide using isopropylamine. The crude compound (10 g) was recrystallized from a mixture of isopropanol and hexane (1:1, v/v). Colorless needles were attained [mp 176°C, $[\alpha]_D^{20} = -21.0°$ ($c = 1.0$)] in methanol.

### Modification of AcSP-APS with ATA (CSP-ATA)

The procedure of Takeda et al.[7] was used for the modification of AcSP-APS di-*N*-succinimidyl oxalate. A mixture containing 2 g (7.04 mmol) of di-*N*-succinimidyl, 0.56 g (7.04 mmol) of pyridine, and 1.94 g (7.04 mmol) of the monoamide ATA in 150 mL of acetonitrile was stirred at room temperature for 12 h. The resulting almost clear solution was cooled to 0°C and added dropwise to a mixture of 4.2 g of AcSP-APS containing 6 mmol —NH₂ groups and 0.7 g (6 mmol) of triethylamine in 20 mL of acetonitrile while stirring. The mixture was maintained at this temperature for 1.5 h and then at room temperature for 1 h. The modified CSP-ATA material was collected by filtra-
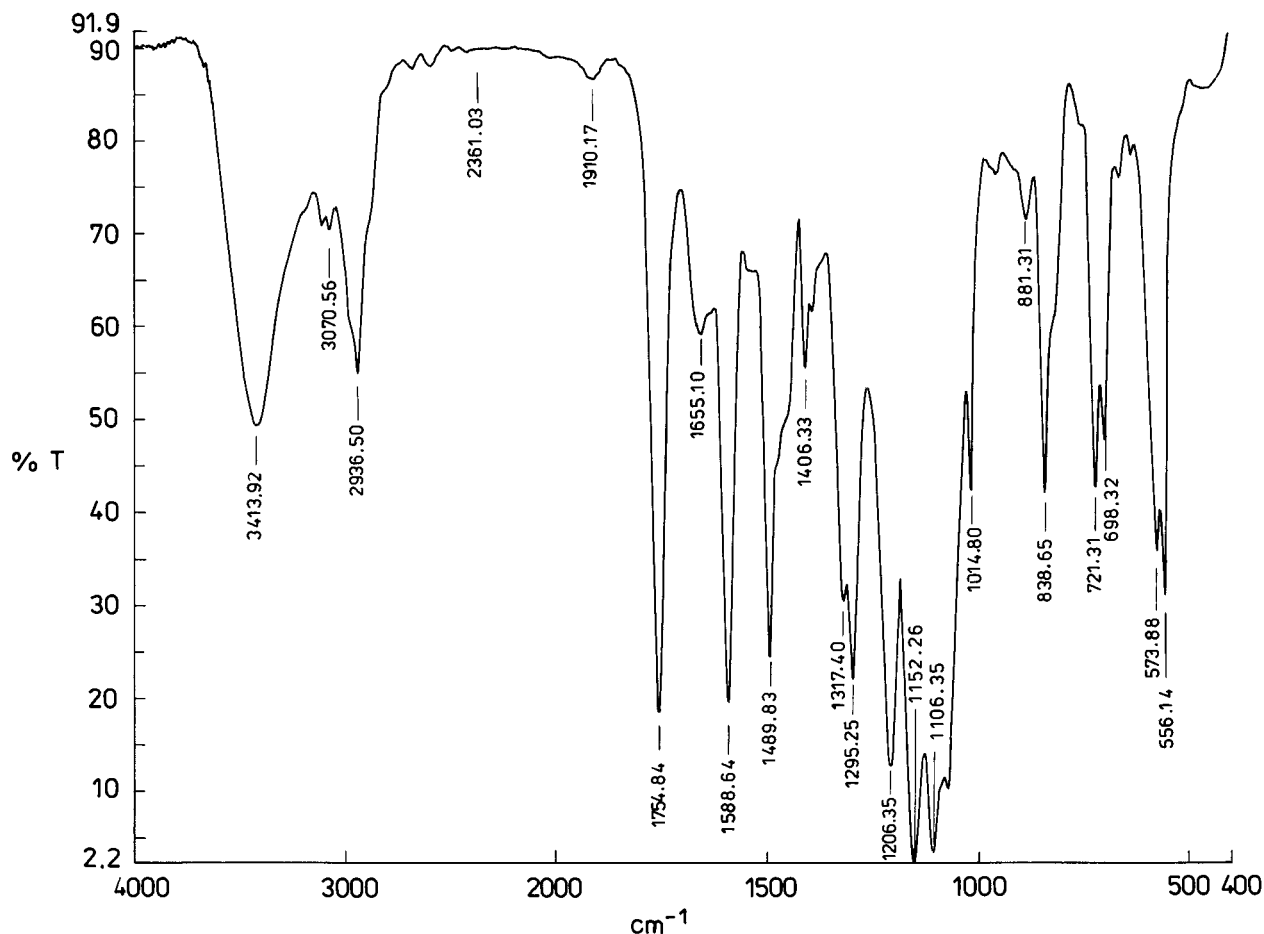
**Figure 1**   FTIR spectra of CSP-TA.

tion; washed with water (500 mL), methanol (200 mL), and acetone (200 mL); and finally dried at room temperature. The elemental anlysis found 2.05% N.

**Hydrolysis of CSP-ATA (CSP-TA)**

To a suspension containing 4 g of modified CSP-ATA in 40 mL of methanol was added 10 mL of 10% $NH_4OH$ at 0°C. The mixture was gently stirred at this temperature for 6 h. The modified beads of the copolymer (CSP-TA) were collected by filtration and washed with water (200 mL), methanol (200 mL), and acetone (200 mL). Finally, they were dried in a vacuum at room temperature. The elemental anlysis found 2.1% N.

**Measurements**

The Fourier transform IR (FTIR) spectra of the monomers and copolymers were run on a Perkin–Elmer model 1725 instrument using KBr pallets. The $^{13}$C-cross polarization with magic angle spinning (CP/MAS)-NMR was conducted on a Bruker 300 MSL CP/MAS instrument operating at 75.47 MHz. The spectra were run with fine powders of glassy beads at room temperature and a Kel-F rotor was used for the MAS. The samples were rotated with a spectra width of 25.000 Hz, the CP time was 22 ms, and the number of scans was in the range of 150–750. Each sample was rotated with two different spin rates, and the spinning side bands were eliminated by comparing the results of the spectra.

Thermograms were run on a Paulik Erdey derivatograph (MOM, Budapest, Hungary). Characterization of the porous structure was made by means of an adsorption analyzer (ASAP 2010 N, Micrometrics Inc.). The determinations were based on the measurements of the adsorption of nitrogen on the surface of the studied sample
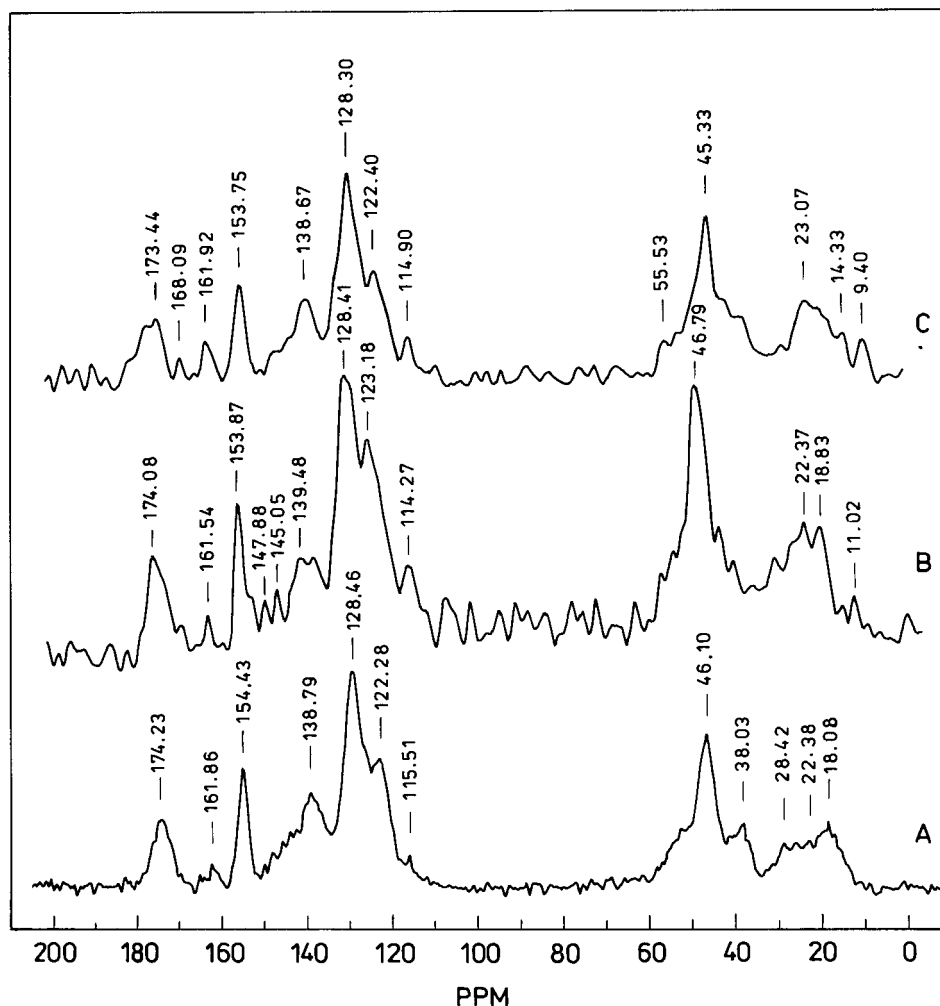
**Figure 2** $^{13}$C-CP/MAS NMR spectra of AcSP-polym-OH (spectrum A), AcSP-APS (spectrum B), and CSP-TA (spectrum C).

while cooling it with liquid nitrogen. The beads were imaged using a LEO 1430 VP numeral scanning electron microscope with a countershaft and an energy dispersive X-ray detector.

## RESULTS AND DISCUSSION

The synthesis of the packing modified by (*R,R*)-tartramide is shown in Scheme 1. The matrix with the pendant —OH groups (AcSP-polym-OH) was activated by APS (step 1). The AcSP-APS was condensed with (*R,R*)-*N*-isopropyldiacetyl tartaric acid monoamide using di-*N*-succinimidyl oxalate (CSP-ATA) in acetonitrile (step 2). Hydrolysis of acetyl groups by NH$_4$OH gave CSP-TA (step 3).

The yield of the modification process was high. The contents of —OH groups in AcSP-polym-OH was 1.48 mmol/g. Elemental analysis confirmed that the modified polymeric beads (CSP-TA) contained 1.43 mmol/g of tartramide moiety.

## IR Spectroscopy

IR spectroscopy is the most widely used technique not only for the chemical reactions performed on the crosslinked polymers but also for structure identification. The FTIR spectra of CSP-TA are shown in Figure 1. The C—H stretching vibrations of the aromatic ring, backbone methylene, methyl, and ethoxy groups were observed at 3100, 3070, and 2936 cm$^{-1}$. The ester carbonyl group

**Table I   Characterization of Porous Structure of Polymeric Matrix (AcSP-polym-OH) and Chiral Phase (CSP-TA)**

| Polymeric Phase | Specific Surface Area (m$^2$/g) | Pore Volume (cm$^2$/g) | Mean Pore Diameter (Å) |
|---|---|---|---|
| AcSP-polym-OH | 134.6 | 0.37 | 55.4 |
| CSP-TA | 124.5 | 0.47 | 77.1 |

gave a sharp band at 1754 cm$^{-1}$ while the amide carbonyl group was at 1655 cm$^{-1}$. The bending vibration of the methyl groups was visible at 1489 cm$^{-1}$. The —SO$_2$ groups gave valency and deformation vibrations at 1152 and 1295 cm$^{-1}$, respectively, and bending and oscillatory vibrations at 556 and 573 cm$^{-1}$, respectively. The bands at 836 and 1070 cm$^{-1}$ were characteristic for the Si—C and Si—O—C bonds, respectively. A sharp band at 3413 cm$^{-1}$, which is characteristic for —OH and —NH groups, was also observed.

## $^{13}$C-CP/MAS-NMR Spectroscopy

In recent years, $^{13}$C-CP/MAS-NMR has been used for characterization of crosslinked insoluble resins. Figure 2 shows the $^{13}$C-CP/MAS-NMR spectra of the AcSP-polym-OH polymeric matrix, silanized (AcSP-APS) copolymer, and copolymer condensed with tartramide (CSP-TA). The spectra showed eight resolved signals at 173.4, 153.7, 138.6, 128.3, 122.4, 45.3, 39.0, and 17.3 ppm for the polymeric matrix [AcSP-polym-OH] and six resolved signals at 9.4, 14.3, 23.0, 41.0, 55.5, and 168.0 ppm for the chiral fragment of the copoly-

mer beads. The methyl groups appeared as a broad peak at 14.3 ppm. The backbone —CH$_2$ groups were visible at 41.0 ppm as a small peak, whereas the secondary carbon of isopropyl groups appeared at 23.0 ppm. The C—O secondary carbons of the tartaric acid gave a signal at 55.5 ppm. The ethoxy groups bonded to Si atoms gave well-resolved peaks at 9.4 ppm. For the amide carbonyl groups a nonintensive signal at 168.0 ppm was observed.

## Porous Structure Characterization

The specific surface areas, pore volume, and mean diameters for the polymeric matrix (AcSP-polym-OH) and modified packings of CSP-TA are presented in Table I. The specific surface area was calculated according to the standard Brunauer–Emmett–Teller[8] method. The pore distribution was calculated from the desorption data using the Barrett–Joyner–Halenda[9] method. Figure 3 presents the curve of the pore volume distribution versus the radii for the modified packing. As follows from the curve and the data in Table I, the specific surface areas of the polymer matrix and
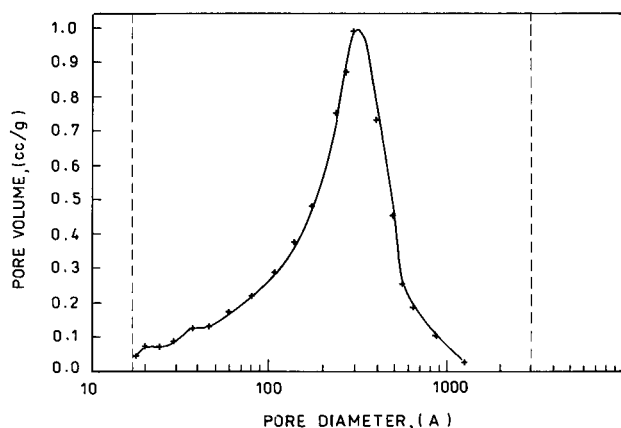


**Figure 3**   The pore volume distribution versus the radii for the modified packing (CSP-TA).
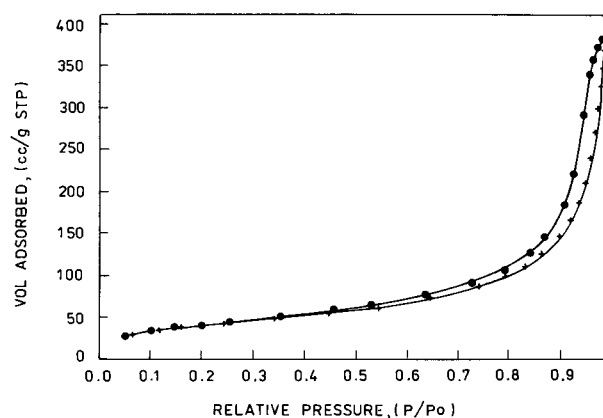


**Figure 4**   The low-temperature isotherms of nitrogen (+) adsorption and (●) desorption for CSP-TA.
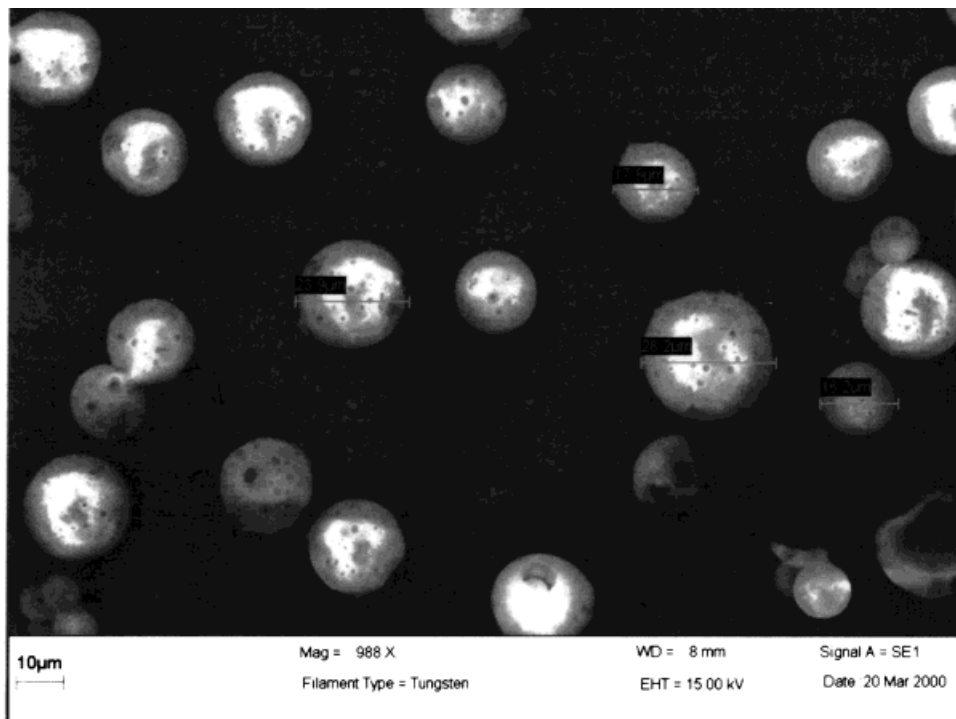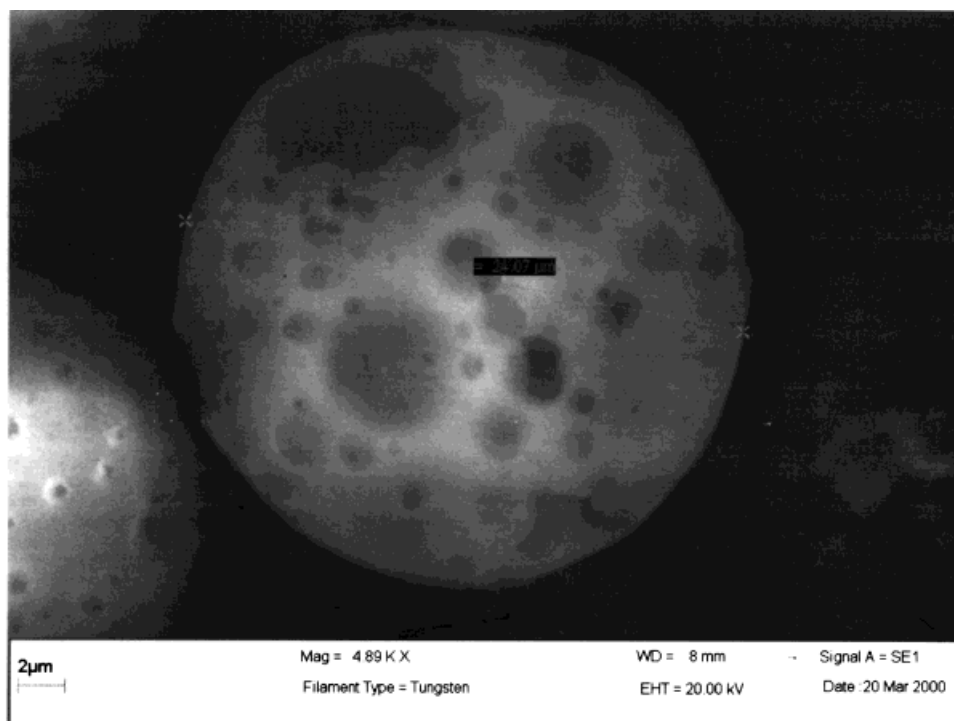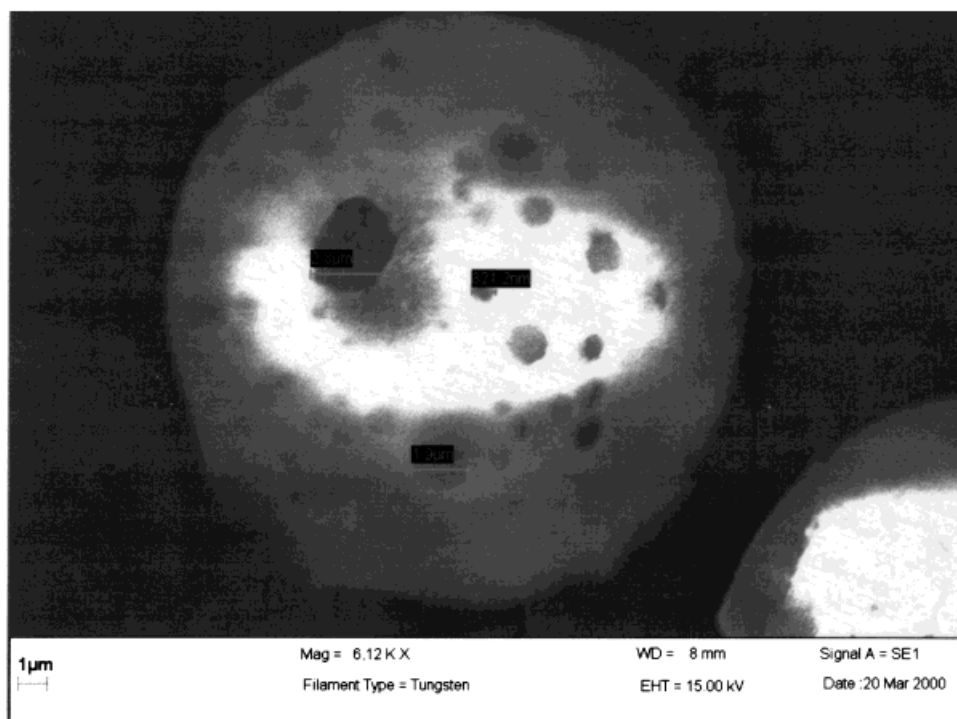
(a)
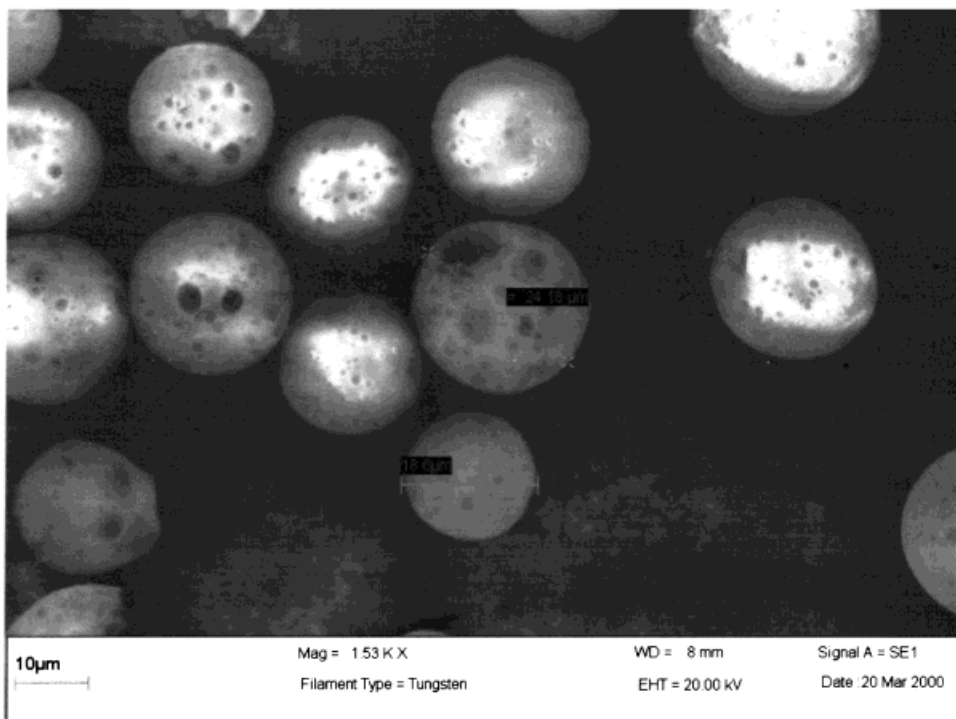


(b)

**Figure 5**   Scanning electron micrographs of the CSP-TA at the following original magnifications: (a) ×988, (b) ×1530, (c) ×4890, and (d) ×6120.

(c)



(d)

**Figure 5**   (*Continued from the previous page*)

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    RONTEC EDWIN WinTools
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                                      Eo:20.0 keV  (TO:35.0  TI:48.0)


                        *** PUzaf results ***
    elem/line   P/B     B       F        c     c(atom)  confid. h
    C  K-ser   Coat? 1.00000 1.00000  51.46    60.03  +- 9.69  d
    N  K-ser         1.00000 1.00000  19.25    19.26  +- 3.48  d
    O  K-ser         1.00000 1.00000  17.43    15.26  +- 2.80  d
    Si K-ser   63.4  1.00718 1.01461   4.32     2.16  +- 0.12  
    S  K-ser   130.9 1.01007 1.00849   7.54     3:29  +- 0.15  
    ------------------------------------------------------------
    standardless                     100.00   100.00    [1s]
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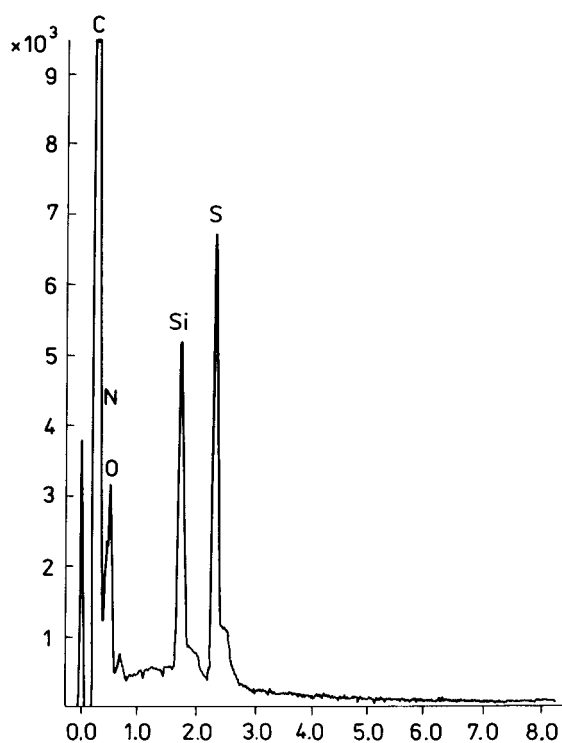


**Figure 6** The roentgenographic analysis of a selected fragment of the CSP-TA surface.

CSP-TA packing were nearly the same. After modification the copolymer pore volume and mean pore diameter were about 10% larger. Figure 4 presents low-temperature isotherms of nitrogen adsorption–desorption. Based on the generally accepted classification of adsorbents,[10] the isotherms obtained for the chiral phase (CSP-TA) can be considered type IV isotherms. The observed hysteresis loops are typical for mesoporous absorbents. Such materials are promising packings for chromatographic columns.

**Scanning Electron Microscopy**

The scanning electron micrographs of CSP-TA beads are shown in Figure 5. The particles had a perfect spherical shape and a porous surface. Figure 6 presents the results of quantitative and qualitative analyses of selected fragments of the packing surface obtained by roentgenographic determinations. From these data (the presence of Si, O, and N atoms) it appears that there were pendant chiral fragments on the surface of the beads.

**Thermogravimetric Analysis**

The thermal behavior of the chiral copolymer CSP-TA was evaluated by dynamic thermal and thermogravimetric analyses. The thermogravimetric curves of CSP-TA are shown in Figure 7. The initial decomposition temperature was noted at 300°C. The final decomposition temperature was 800°C. The chiral phase decomposed in two stages. The first stage decomposition was observed in the range of 300–370°C and the second
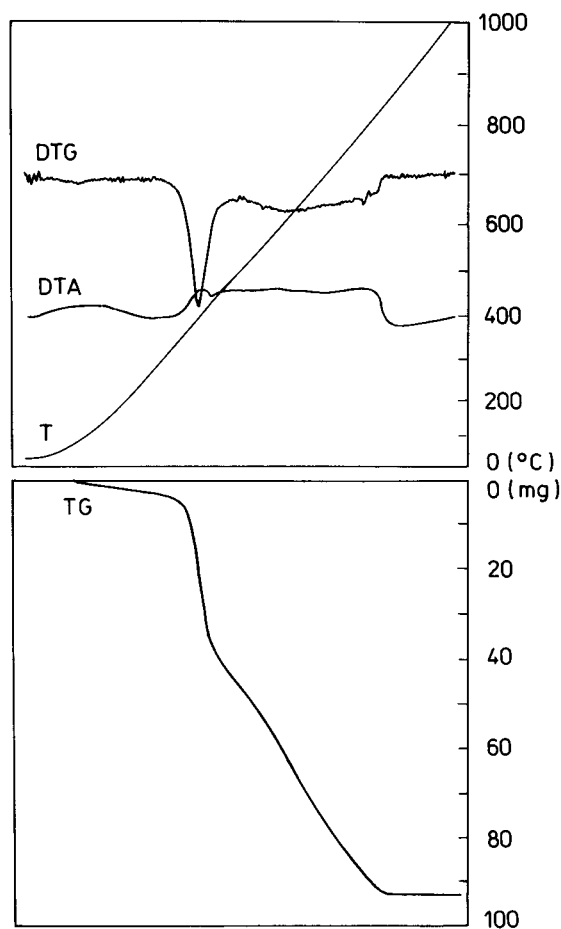


**Figure 7** Thermogravimetric analysis of the chiral polymeric stationary phase (CSP-TA).

**Table II   Swelling Studies of CSP-TA**

| Solvent | $m$ (g) | $V_0$ (mL) | $V$ (mL) |
|---|---|---|---|
| Acetone | 3.28 | 3.70 | 4.36 |
| Dichloromethane | 4.64 | 3.90 | 5.00 |
| Methanol | 2.78 | 4.00 | 5.00 |
| 1,4-Dioxane | 3.30 | 4.00 | 4.50 |
| Hexane | 3.28 | 4.00 | 4.25 |
| Isopropanol | 4.00 | 4.00 | 4.50 |

$m$, the weight of the solvent absorbent per 1 g of a dry chiral phase; $V_0$, the volume of 1 g of a dry chiral phase; and $V$, the volume of 1 g of a dry chiral phase after swelling.

one took place between 370 and 790°C. After decomposition there was about 5% inorganic substance remaining. This was probably silicide condensed with the polymeric matrix during the modification process.

### Swelling Studies

The accessibility of functional groups is associated with swelling.[11] The samples were swollen in a few solvents for 1 h to investigate the swelling behavior. The excess solvents were removed by centrifugal methods.[12] The results were expressed as the weight of the solvent absorbent per 1 g of the dry copolymer and the change of volume after swelling. As follows from the results in Table II, the volume of the copolymer modified with the chiral factor was increased insignificantly.

The CSP-TA absorbed a large amount of the solvents, but its volume was rather constant.

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